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Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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incidence

Malignant pleural mesothelioma (MPM) is a rare tumour. The incidence is 1.25/100 000 in Great Britain and 1.1/100 000 in Germany. Within the next 20 years the incidence is estimated to double in many countries. Exposure to asbestos is a well-established aetiological factor for MPM, with occupational exposure being documented in 70%–80% of those affected.

diagnosis

Patients typically present with shortness of breath due to pleural effusion or chest pain in a more advanced stage. The diagnosis is usually suggested by imaging studies (unilateral pleural thickening; pleural effusion). An occupational history must be obtained.

Cytological examination of the effusion can be diagnostic, but often shows equivocal results. Therefore, histology, including immunohistochemistry, is the gold standard. Pleuroscopy, a video-assisted surgical procedure or open pleural biopsy in a fused pleural space may be necessary to provide sufficient material for accurate histological diagnosis. There are three main histological types (epithelial, sarcomatous and mixed) with ~60% being epithelial.

Data suggest the possible contribution of serum mesothelin-related proteins and osteopontin as useful markers to support the diagnosis of mesothelioma; however, the precise role of these markers is yet to be defined.

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staging and risk assessment

Clinical staging is based on the CT scan of the chest. However, the translation of the images into TNM stages is often not conclusive. Mediastinoscopy and video-assisted thoracoscopy may be useful in determining the stage. Accurate initial staging is essential to provide both prognostic information and guidance on the most appropriate therapeutic options. Several different staging systems exist, among them the international IMIG staging system for MPM which emphasizes the extent of disease post-surgery in a traditional TNM system and stratifies patients into prognostic categories similar to those shown in Table 1.

The European Organization for Research and Treatment of Cancer prognostic scores may be used. They include performance status, gender, certainty of histology, histological type and white blood count.

MPM rarely metastasizes to distant sites but most patients present with locally advanced disease. The use of PET scan to rule out extra-thoracic metastasis in patients considered for radical treatment is under investigation and findings seem promising.

treatment

surgery

Various surgical procedures have been studied with varying degrees of success.

Extra-pleural pneumonectomy (EPP) with resection of the hemi-diaphragm and the pericardium *en bloc* has the potential for a radical treatment and this approach is generally combined with neoadjuvant or adjuvant chemotherapy and/or adjuvant radiotherapy. Surgery, the appropriateness of which is still under consideration, should only be performed on selected patients by experienced thoracic surgeons in the context of a multidisciplinary team and preferably as part of a clinical trial [III, A]. Selection criteria include good performance status, and earlier stage disease with not more than localized involvement of the thoracic wall, and adequate cardiopulmonary function. The inclusion of

Table 1. TNM staging system for MPM

Stage	TNM	Comments
Ia	T1a N0 M0	Primary tumour limited to ipsilateral parietal pleura
Ib	T1b N0 M0	As stage Ia plus focal involvement of visceral pleura
II	T2 N0 M0	As stage Ia or Ib plus confluent involvement of diaphragm or visceral pleura or involvement of the lung
III	Any T3 M0	Locally advanced tumour
	Any N1 M0	Ipsilateral, bronchopulmonary or hilar lymph node involvement
	Any N2 M0	Subcarinal or ipsilateral mediastinal lymph node involvement
IV	Any T4	Locally advanced technically unresectable tumour
	Any N3	Contralateral mediastinal, internal mammary, and ipsilateral or contralateral supraclavicular lymph node involvement
	Any M1	Distant metastases

patients with N2 or sarcomatoid disease is controversial. Pleurectomy/decortication may be indicated for elderly patients, at early stages or when EPP would leave macroscopic tumour behind.

To optimally palliate patients from dyspnea and pain, local procedures to control pleural effusion include parietal pleurectomy or talc pleurodesis.

radiotherapy

The use of curative intent hemithoracic radiotherapy has been limited because of the difficulty of irradiating such a large target volume to high doses without exceeding the tolerance of the adjacent normal tissues, especially the (homolateral) lung. The exact role of definitive radiotherapy in the multimodality approach of MPM is currently under investigation. Nevertheless, in an attempt to improve local control after EPP, it has been shown feasible to deliver radiotherapy doses of >45 Gy with both 3D conformal (3D-CRT) and intensity-modulated radiotherapy (IMRT). However, caution must be exercised regarding the exposure of the contralateral lung to low-dose irradiation, especially when using IMRT [III, B].

In the palliative setting, radiotherapy can be delivered locally in view of pain control or prevention of obstructive symptoms [IV, C]. As mesothelioma invades the tracts made by chest instrumentation, prophylactic irradiation to the intervention tracts (PIT) has been advocated to reduce the incidence of port metastases. In the absence of unambiguous prospective data—the consequence of randomized trials with small patient numbers, different results according to histology and highly variable RT techniques—however, it remains impossible to draw definitive conclusions regarding its efficacy [II, C].

chemotherapy

Platinum analogues, doxorubicin and some antimetabolites (methotrexate, raltitrexed, pemetrexed) have shown modest single-agent activity [III, B].

The combinations of both pemetrexed/cisplatin, and to a smaller extent raltitrexed/cisplatin, have been shown to improve survival as well as lung function and symptom control in comparison with cisplatin alone in randomized trials [II, A]. The combination of pemetrexed/carboplatin is an alternative effective therapy [III, A]

A phase III trial evaluated second-line pemetrexed versus best supportive care in patients not previously exposed to this agent and found a longer time to disease progression in the chemotherapy arm. Since vinorelbine or gemcitabine have first-line activity they might be a reasonable choice in second-line therapy. One study on 63 patients treated with vinorelbine reported a 16% response rate and median survival of 9.6 months [III, A].

If extrapleural pneumonectomy is planned, platinum-based neoadjuvant or adjuvant combination chemotherapy should be considered.

response evaluation

Response evaluation using CT scan is recommended after two to three chemotherapy cycles and the modified RECIST criteria should be applied. Volumetric measurements are under investigation.

follow-up

Follow-up consists of clinical evaluation, with particular attention to symptoms or chest wall recurrence, and chest CT as needed.

note

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

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